

The miliyer tuberculosis mimirating oropharynx carcinoma in a patient using anti-TNF: Review of the literature

Tuberculosis a patient using anti-TNF

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Abstract

Tumor necrosis factor-alpha (TNF- α) inhibitors are biological agents frequently used in many clinics, especially in rheumatology. In this article, we report a 59-year-old woman with RA who received adalimumab treatment for five years. The diagnosis and treatment of miliary tuberculosis secondary to irregular latent tuberculosis (TB) treatment with atypical symptoms will be discussed. In the literature, patients with a similar diagnosis who developed TB during treatment have also been presented. Patients at risk of latent TB who receive anti-TNF therapy should be closely monitored and the importance of prophylaxis should be emphasized.

Keywords

Anti-Tnf Treatment, Latent Tuberculosis, Miliary Tuberculosis

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Introduction

With the introduction of tumor necrosis factor-alpha inhibitors (TNFAI) into clinical use, significant success has been achieved in treating many inflammatory diseases, especially rheumatoid arthritis (RA), seronegative spondyloarthropathy, and inflammatory bowel diseases. Unlike many other anti-inflammatory drugs, TNFAI acts through a targeted therapy mechanism. However, many remarkable side effects associated with these drugs are also reported. These include mycobacterial infections, especially tuberculosis (TB), other viral, fungal, or bacterial infections, infusion reactions, local reactions at the injection site, heart failure, demyelinating diseases, triggering of autoimmunity, and malignancy [1].

Infliximab, a chimeric monoclonal antibody containing the murine Fab region; fully humanized monoclonal antibodies adalimumab and golimumab; certolizumab, a pegylated human Fab fragment, and etanercept, a fusion protein of the extracellular domain of Tumor necrosis factor receptor 2 (TNFR2) and the human immunoglobulin (Ig)1 Fc fragment, are TNF- α blockers approved for clinical use [2].

The risk of infection is thought to be higher, especially in the first year of treatment. It has been reported that the monoclonal antibodies adalimumab and infliximab are more prone to infections than the soluble receptor etanercept [3].

A meta-analysis summarizing the risk of TB associated with TNF- α blockade in thousands of patients with RA or other inflammatory diseases has shown an approximately four-fold increase in TB in those treated with TNF- α blockers compared with other treatments [4]. Here, we will talk about a case of miliary TB presenting with atypical symptoms such as sore throat and hoarseness, using adalimumab, a monoclonal antibody, with a diagnosis of RA.

In this article, we will discuss a case of TB associated with anti-TNF use and review similar cases in the literature.

Material and Methods

A 59-year-old female patient, diagnosed with seronegative RA for seven years, was started on adalimumab treatment five years previously after failing to respond to non-biologic disease-modifying anti-rheumatic drugs (DMARDs) and was in clinical remission for RA. Three years ago, after the patient's PPD (purified protein derivative) test was 11 mm, the patient was started on isoniazid (INH). The patient used INH for three months, then took a two-month break due to coronavirus disease-2019 (COVID-19); and then continued for seven more months. The treatment was completed in 9 months. When the patient developed complaints of sore throat and hoarseness three years after prophylaxis, acute upper respiratory tract infection was considered and antibiotic therapy was started. The patient, whose complaints did not improve, applied for a routine rheumatology check-up. In laboratory parameters; C-reactive protein: 4.62 mg/L (0-5), erythrocyte sedimentation rate: 53 mm/h (0-20), white blood cell count: $5.02 \times 10^3/\mu\text{l}$, platelet count: $267 \times 10^3/\mu\text{l}$, and hemoglobin: 13.1 g/dl. The patient attended the Department of Otolaryngology with the current complaints. Upon neck computed tomography (CT) showing a mass lesion measuring 26x14 mm in the oropharynx (figure 1A), a biopsy was planned with suspicion of malignancy in the oropharynx,

and the biopsy result was reported as "granulomatous inflammatory event accompanied by focal ulceration." Thorax CT was requested for the patient with the preliminary diagnosis of TB. In thorax CT, In the right axillary fossa, several enlarged lymph nodes, the largest of which was 9x12 mm, with thick cortex, whose fatty hilus could not be discerned, and LAPs, the largest of which was subcarinal and 20x30 mm in size, were observed in the mediastinum, in the prevascular area, in both upper paratracheal and lower right paratracheal areas, and in both hilar regions in the subcarinal area. In evaluating the lung parenchyma areas, more prominent widespread budded tree appearances were observed in the upper lobes of both lungs (active TB?)(figure 1B/ 1C).

Paramediastinal atelectatic density change was observed in the anterior upper lobe of the left lung. The patient's transbronchial biopsy result was reported as a granulomatous inflammatory event by the chest diseases department, and quadruple anti-TB treatment was started after the lavage taken from the patient also showed *Mycobacterium Tuberculosis* growth. The patient was commenced on isoniazid, rifampicin (RIF), ethambutol, and pyrazinamide, and since she was not stable during follow-up, dual treatment with INH and RIF was started two months later. She is currently in the ninth month of her treatment, which is planned to be completed in 12 months. All radiological imaging studies and laboratory tests of the patient were performed at our institution.

A literature search with the keywords "adalimumab", "rheumatoid arthritis" "tuberculosis", and yielded 67 results in PUBMED and 40 results in SCOPUS over the last 10 years. When the results were screened, there were 15 RA patients who developed tuberculosis under adalimumab (Table 1).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Results

When the results were screened, there were 15 RA patients who developed tuberculosis under adalimumab. Most of the cases were female patients. The mean age was 64 years, and the mean interval between adalimumab treatment and TB was 40.7 months. Similarly, TB was observed in our case 48 months after prophylaxis. Four miliary TB, 3 peritoneal TB, 4 pulmonary TB, 2 tongue TB, 1 brain TB, and 1 ganglionary TB were observed. As in our case, pulmonary TB is common in the literature. Seven patients had a negative TST or IGST, 3 had a positive TST or IGST, 2 did not receive prophylaxis and 5 did not report results.

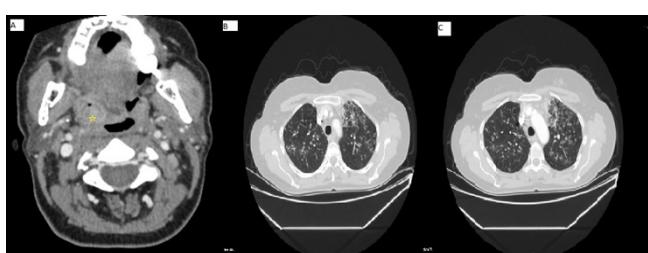


Figure 1. FIGURE A: Mass lesion visible in the oropharynx on neck computed tomography (CT)

FIGURE B AND C: Common tree in bud appearances in lung parenchyma regions on thorax

Table 1. Patients who develop tuberculosis and their characteristics

Gender	Age	Disease duration	TST/IGST quantiferon	Diagnosis Method	Duration of exposure to drug	Outcome	Reference
F	71	20 y	-/-	Tongue bx	6 y	Tongue TB	[9]
F	73	2 y	-	Abdominal CT paracenteses	11 m	Peritoneal tb	[10]
F	65	10 m	-	?	5 y	Milier TB	[11]
M	39	25 m	-	?	4 y	Pulmonary TB	[11]
F	48	30 m	-	?	5 y	Ganglionar TB	[11]
F	64	27 y	+ (don't take proflaxy)	Chest CT, Brain MRI, TB PCR	5 y	Milier TB; Brain tb	[12]
F	79	1 y	?	Colonoscopic bx, Chest CT, Abdominal CT	6 y	Intestinal TB, Pulmonary TB	[13]
F	72	11 y	-	Chest CT, Abdominal CT	6 m	Milier TB	[14]
M	?	?	+	?	?	?	[15]
F	62	?	?	Tongue bx and culture	?	Tongue tuberculosis	[16]
F	65	?	+ (don't take proflaxy)	Chest CT/sputum ARB Abdominal CT/splenic bx	?	Disseminated histoplasmosis, Milier TB	[17]
F	62	?	-	?	22.7 m	TB pleurisy	[18]
F	61	?	?	Culture	5 m	Extrapulmonary	[19]
F	71	?	?	Clinical	32 m	Pulmonary TB	[19]

CT: Computerized tomography, MRI: Magnetic resonance imaging, PCR: Polymerase chain reaction, ARB: Acid-resistant bacillus Bx: Biopsy, y: years, m: month

Although TST or IGST was positive, miliary and atypical localized TB was observed in patients who did not receive prophylaxis. As in the literature and in our case, negative TST and IGST are insufficient to predict the development of TB.

Discussion

Rheumatoid arthritis is one of the most common chronic inflammatory diseases that can lead to bone and cartilage damage, as well as disability. TNFAI treatment has been established as an effective therapeutic strategy in patients with RA. TNF- α is a pro-inflammatory cytokine that plays a vital role in the pathogenesis of chronic immune-mediated diseases. Five TNFAIs have been approved for clinical use in rheumatology practice. These are infliximab, etanercept, adalimumab, certolizumab, and golimumab [5].

TNFAI drugs are generally well tolerated; However, many potentially serious adverse effects have also been reported. Long-term use of these drugs has been associated with the risk of malignancies and serious infections such as TB [6].

It is recommended to screen for latent TB infection before starting treatment in patients for whom TNFAI is planned. Although there is no gold standard test for this purpose, interferon-gamma release test (IGST) and tuberculin skin test (TST) can be used for screening purposes. If induration is ≥ 5 mm in TST, it is considered positive, and protective treatment is applied. It seems appropriate to screen patients for whom latent TB is not detected initially and TNFAI treatment is initiated annually for latent TB infection [7, 8]. Prophylaxis was started in our patient when the TST was 11 mm, and there was a disruption in his treatment due to COVID-19 infection. Therefore, her prophylaxis was negatively affected.

Cases of TB despite negative TST or IGST have been observed in the literature. Miliary or pulmonary TB is frequently seen, but atypical localisations are also noteworthy, although rare.

In conclusion, the risk of TB is increased in patients receiving TNFAI, especially infliximab and adalimumab. As seen in the literature, pulmonary and miliary TB are frequently observed. Screening for latent TB with TST or IGST before treatment

should not be neglected as it reduces the risk of TB; however, even with a negative test result, patients should be closely monitored and informed. TB infection may present with atypical symptoms such as cough, fever, sore throat, weight loss, and hoarseness. Laboratory and imaging findings in patients with atypical presentations may initially cause diagnostic confusion. Therefore, in cases where the diagnosis is suspected, tissue biopsy may be helpful in the diagnosis if necessary.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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